Pathology

Subject : Pathology

Lec no : 13

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السلام عليكم رفعة

اانا شخصيًا حسيت سرد المعلومات بالسلايدات مش واضح كفاية رحت عملت تغيير بسرد المعلومات + زودت نتفة معلومات بتساعدكم بالفهم أكيد هي مش للحفظ بس اقرأوهم للفهم لانو لو حاولتوا تحفظو ابدون فهم ما في فايدة من دراستكم برجع بأكد مش للحفظ وبس بالتوفيق ان شاء لله

Effects of inflammation :

protective mechanism → kill / repair / prevent

وقائية

A- Beneficial effects :

افرازات

These act partly through the flow of exudates into the tissue & partly by the phagocytic & microbial effects of migrated WBCs. :

(1)Dilution of toxins : exudates dilutes chemical and bacterial toxins & enhance their carriage by lymphatics.

تخفيف التأثير

(2)Protective antibodies : The proteins present in the exudates include antibodies , which have been already present in the plasma as a result of previous infection or immunization. These antibodies attack injurious agents in an attempt to destroy them immunologically.

(antibody attack the antigen)

هاد شرح توضيحي ضفته لانو السلايدات مش واضحة

Inflammation has beneficial effects that involve the flow of exudates into the tissue and the actions of white blood cells (WBCs). Firstly, the ① dilution of toxins occurs as exudates dilute chemical and bacterial toxins, facilitating their removal by the lymphatic system. Additionally, ② protective antibodies present in the exudates, generated from prior infections or immunization, contribute to the immune response. These antibodies target injurious agents, aiming to destroy them immunologically, thereby enhancing the overall defense against harmful substances.

للالتهاب تأثيرات مفيدة تتضمن تدفق الإفرازات إلى الأنسجة وعمل خلايا الدم البيضاء. أولاً، يحدث تخفيف السموم حيث تعمل الإفرازات على تخفيف السموم الكيميائية والبكتيرية، مما يسهل إزالتها عن طريق الجهاز اللمفاوي. بالإضافة إلى ذلك، تساهم الأجسام المضادة الواقية الموجودة في الإفرازات، الناتجة عن العدوى السابقة أو التحصين، في الاستجابة المناعية. تستهدف هذه الأجسام المضادة العوامل الضارة، بهدف تدميرها مناعيًا، وبالتالي تعزيز الدفاع الشامل ضد المواد الضارة.

(3)*Fibrin formation* : Fibrinogen of the blood is included in the exudates which is transformed into fibrin . A network of the deposited fibrin is seen in the inflamed tissue forming a mechanical barrier that precludes the movement & spread of bacteria, it may also aid in their phagocytosis.

(4) Promotion of immunity :

Bacteria in the inflammatory exudates , whether free or phagocytosed , are carried to the lymph nodes by lymphatics. There they mount an immune response, which provides antibodies & cellular mechanisms that may appear after few days and may remain for years. These immunological mechanisms help destroy microbial agents.

In inflammation, fibrinogen from the blood becomes part of the exudates and transforms into fibrin. This deposited fibrin creates a network in the inflamed tissue, serving as a mechanical barrier. This barrier restricts the movement and spread of bacteria and may also assist in their phagocytosis, contributing to the containment and elimination of the infectious agents in the affected area.

في الالتهاب، يصبح الفيبرينوجين الموجود في الدم جزءًا من الإفرازات ويتحول إلى الفيبرين. يخلق هذا الفيبرين المترسب شبكة في الأنسجة الملتهبة، تعمل كحاجز ميكانيكي. يقيد هذا الحاجز حركة البكتيريا وانتشارها وقد يساعد أيضًا في البلعمة، مما يساهم في احتواء العوامل المعدية والقضاء عليها في المنطقة المصابة.

In the promotion of immunity during inflammation, bacteria in the inflammatory exudates, whether free or phagocytosed, are transported to the lymph nodes by lymphatics. In the lymph nodes, an immune response is mounted, generating antibodies and cellular mechanisms. These immune components may develop a few days after exposure and can persist for years, contributing to the ongoing defense against microbial agents and facilitating the destruction of these pathogens over an extended period.

لتعزيز المناعة أثناء الالتهاب، يتم نقل البكتيريا الموجودة في الإفرازات الالتهابية، سواء كانت حرة أو مبتلعة، إلى العقد الليمفاوية عن طريق الأوعية الليمفاوية. في الغدد الليمفاوية، يتم تركيب الاستجابة المناعية، وتوليد الأجسام المضادة والآليات الخلوية. قد تتطور هذه المكونات المناعية بعد أيام قليلة من التعرض ويمكن أن تستمر لسنوات، مما يساهم في الدفاع المستمر ضد العوامل الميكروبية وتسهيل تدمير مسببات الأمراض هذه على مدى فترة طويلة.

B-Harmful effects :

1 **Swelling :** of acutely inflamed tissue may have serious mechanical effects e.g in acute laryngitis causes suffocation in children

2 **Rise in tissue pressure:**

Inflammation when is confined within a restricted space cannot expand, the result is an increase in tissue pressure and this interferes with cell function and the blood flow, the latter leads to ischemic injury ,e.g. encephalitis and meningitis both cause increased intra cranial pressure and even death.

Similarly osteomyelitis leads to bone necrosis due to ischemia caused by pressure on blood vessels.

3 **Sever allergic reaction:** e.g. to pollen may cause sever asthma & dyspnoea , this may sometimes be so sever as to cause death due to asphyxia caused by laryngeal edema.

Swelling in acutely inflamed tissue can lead to significant mechanical effects, such as in acute laryngitis in children. In this condition, the swelling can obstruct the airways, causing difficulties in breathing and potentially leading to acute suffocation. The increased tissue volume during inflammation, especially in sensitive areas like the larynx, highlights the importance of managing inflammation promptly to prevent severe complications, particularly in vulnerable populations like children.

يمكن أن يؤدي التورم في الأنسجة الملتهبة بشكل حاد إلى تأثيرات ميكانيكية كبيرة، كما هو الحال في التهاب الحنجرة الحاد عند الأطفال. في هذه الحالة، يمكن أن يؤدي التورم إلى انسداد المسالك الهوائية، مما يسبب صعوبات في التنفس وربما يؤدي إلى الاختناق الحاد. إن زيادة حجم الأنسجة أثناء الالتهاب، وخاصة في المناطق الحساسة مثل الحنجرة، يسلط الضوء على أهمية إدارة الالتهاب على الفور لمنع المضاعفات الشديدة، وخاصة في الفئات السكانية الضعيفة مثل الأطفال.

Inflammation confined within a limited space can cause a rise in tissue pressure, disrupting cell function and blood flow. This increase in pressure may result in ischemic injury, as seen in conditions like encephalitis and meningitis, leading to elevated intracranial pressure and, in severe cases, death. Similarly, osteomyelitis can lead to bone necrosis due to ischemia caused by pressure on blood vessels. Managing inflammation is crucial to prevent these complications and maintain proper tissue function and blood flow.

يمكن أن يسبب الالتهاب المحصور في مساحة محدودة ارتفاعًا في ضغط الأنسجة، مما يعطل وظيفة الخلايا وتدفق الدم. قد تؤدي هذه الزيادة في الضغط إلى إصابة إقفارية، كما يظهر في حالات مثل التهاب الدماغ والتهاب السحايا، مما يؤدي إلى ارتفاع الضغط داخل الجمجمة، وفي الحالات الشديدة، الوفاة. وبالمثل، يمكن أن يؤدي التهاب العظم والنقي إلى نخر العظام بسبب نقص التروية الناتج عن الضغط على الأوعية الدموية. تعد إدارة الالتهاب أمرًا بالغ الأهمية لمنع هذه المضاعفات والحفاظ على وظيفة الأنسجة المناسبة وتدفق الدم.

A severe allergic reaction, such as to pollen, can result in intense asthma and dyspnea. In some cases, the reaction can be so severe that it leads to death due to asphyxia caused by laryngeal edema. This highlights the critical nature of managing severe allergic responses promptly, as they can have life-threatening implications, particularly when affecting the airways and causing respiratory distress.

يمكن أن يؤدي رد الفعل التحسسي الشديد، مثل حساسية حبوب اللقاح، إلى الربو الشديد وضيق التنفس. في بعض الحالات، يمكن أن يكون رد الفعل شديدًا لدرجة أنه يؤدي إلى الوفاة بسبب الاختناق الناجم عن الوذمة الحنجرية. وهذا يسلط الضوء على الطبيعة الحرجة لإدارة الاستجابات التحسسية الشديدة على الفور، حيث يمكن أن يكون لها آثار تهدد الحياة، خاصة عندما تؤثر على الشعب الهوائية وتسبب ضائقة تنفسية.

SYSTEMIC EFFECTS OF INFLAMMATION

- These effects are collectively called **acute-phase reaction** .
- They include **fever, malaise** (feeling of being sick), **anorexia** (loss of apatite), **insomnia, hypotension**, accelerated degradation of skeletal muscle proteins,increased hepatic synthesis of a variety of proteins (e.g., complement & coagulation proteins), & alteration in the circulating WBC as **leukocytosis** .
- The most important mediators of the acute-phase reaction are the cytokines **TNF, IL-1, & IL-6,** produced mainly by WBC in response to infection, or to immune & toxic injury, & are released systemically, frequently in a cascade.
- **TNF & IL-1** both act on the **thermoregulatory center of the hypothalamus**- via local PGE production to induce **fever** .

الشرح هون كثير كثير حلووووو وترجمتها تحت

leukocytosis, an increase in the number of white blood cells (WBCs), as part of the acute-phase reaction. The key mediators of this response are cytokines, particularly Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). These cytokines are predominantly produced by white blood cells in response to infection or immune and toxic injury.

During an inflammatory cascade, these cytokines are released systemically, initiating a series of events. TNF, IL-1, and IL-6 play pivotal roles in orchestrating the acute-phase reaction, influencing various physiological processes. This includes stimulating the liver to synthesize acute-phase proteins such as complement and coagulation proteins. Additionally, the release of these cytokines contributes to fever, malaise, and alterations in circulating white blood cells, collectively shaping the body's response to infection or injury.

Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1) exert their influence on the thermoregulatory center of the hypothalamus to induce fever. This process is mediated through the local production of prostaglandin E (PGE).

When the body detects an infection or injury, immune cells release TNF and IL-1. These cytokines then signal the hypothalamus, which acts as the body's thermostat, regulating temperature. In response to TNF and IL-1, the hypothalamus initiates a cascade of events leading to the synthesis of prostaglandins, particularly PGE.

PGE, in turn, influences the hypothalamus to raise the set-point for body temperature. This results in physiological changes such as vasoconstriction and shivering, aiming to increase body temperature and create an environment less favorable for the growth of infectious agents. The induced fever is a protective response, part of the body's strategy to enhance immune function and combat the underlying threat.

زيادة عدد الكريات البيضاء، وهي زيادة في عدد خلايا الدم البيضاء (WBCs)، كجزء من تفاعل المرحلة الحادة. الوسطاء الرئيسيون لهذه الاستجابة هم السيتوكينات، وخاصة عامل نخر الورم (TNF)، والإنترلوكين-1 (IL-1)، والإنترلوكين-6 (IL-6). يتم إنتاج هذه السيتوكينات في الغالب بواسطة خلايا الدم البيضاء استجابةً للعدوى أو الإصابة المناعية والسامة.

أثناء سلسلة الالتهابات، يتم إطلاق هذه السيتوكينات بشكل منهجي، مما يؤدي إلى بدء سلسلة من الأحداث. يلعب TNF وIL-1 وIL-6 أدوارًا محورية في تنسيق تفاعل المرحلة الحادة، مما يؤثر على العمليات الفسيولوجية المختلفة. يتضمن ذلك تحفيز الكبد لتخليق بروتينات المرحلة الحادة مثل البروتينات التكميلية وبروتينات التخثر. بالإضافة إلى ذلك، يساهم إطلاق هذه السيتوكينات في الحمى والشعور بالضيق والتغيرات في خلايا الدم البيضاء المنتشرة، مما يشكل بشكل جماعي استجابة الجسم للعدوى أو الإصابة.

يمارس عامل نخر الورم (TNF) والإنترلوكين-1 (IL-1) تأثيرهما على مركز التنظيم الحراري في منطقة ما تحت المهاد للحث على الحمى. تتم هذه العملية من خلال الإنتاج المحلي للبروستاجلاندين E (PGE).

عندما يكتشف الجسم عدوى أو إصابة، تطلق الخلايا المناعية TNF و IL-1. تقوم هذه السيتوكينات بعد ذلك بإرسال إشارة إلى منطقة ما تحت المهاد، الذي يعمل بمثابة منظم حرارة الجسم، وينظم درجة الحرارة. استجابة لـ TNF و IL-1، يبدأ منطقة ما تحت المهاد سلسلة من الأحداث التي تؤدي إلى تخليق البروستاجلاندين، وخاصة PGE.

يؤثر PGE بدوره على منطقة ما تحت المهاد لرفع نقطة ضبط درجة حرارة الجسم. وينتج عن ذلك تغيرات فسيولوجية مثل انقباض الأوعية الدموية والارتعاش، بهدف زيادة درجة حرارة الجسم وخلق بيئة أقل ملاءمة لنمو العوامل المعدية. الحمى المستحثة هي استجابة وقائية، وهي جزء من استراتيجية الجسم لتعزيز وظيفة المناعة ومكافحة التهديد الأساسي.

signal → ↑ proteins.

- **IL-6 stimulates** the hepatic synthesis of several plasma proteins,

(1)**Fibrinogen; elevated fibrinogen levels** cause RBC to agglutinate more readily, explaining why inflammation is associated **with a higher ESR .**

(2)**C-reactive protein (CRP)** **&**

(3)**serum amyloid A (SAA) proteins,** both bind to microbial cell walls, & they may act as **opsonins** & fix complement, thus promoting the elimination of the microbes.

- **Leukocytosis** (**increased, mature, white blood cell count in blood**) is a common feature of inflammatory reactions, especially those induced by bacterial infection.

- WBC count typically increases from **a normal 4,000 to 10,000 to 15,000 - 20,000 cells per micro liter,** but may climb as high as 40,000 to 100,000, a so-called **Leukemoid (leukemia-like) reaction**

Interleukin-6 (IL-6) plays a significant role in stimulating the hepatic synthesis of various plasma proteins. These include:

1. **Fibrinogen:** Elevated fibrinogen levels contribute to increased erythrocyte sedimentation rate (ESR) during inflammation. This occurs because heightened fibrinogen causes red blood cells to agglutinate more readily, a phenomenon observed in inflammatory conditions.

2. **C-reactive protein (CRP):** CRP is one of the acute-phase proteins synthesized by the liver in response to IL-6. It, along with Serum Amyloid A (SAA) proteins, has the ability to bind to microbial cell walls. Furthermore, CRP and SAA may act as opsonins, enhancing phagocytosis, and they can fix complement, thereby promoting the elimination of microbes.

In summary, IL-6-driven synthesis of these plasma proteins contributes to various aspects of the immune response during inflammation, from influencing ESR to enhancing the elimination of microbes through opsonization and complement fixation.

Leukocytosis, characterized by an elevated count of mature white blood cells in the blood, is a common response in inflammatory reactions, particularly those triggered by bacterial infections. The typical WBC count increases from the normal range of 4,000 to 10,000 cells per microliter, reaching levels of 15,000 to 20,000 cells per microliter. In more extreme cases, it may climb as high as 40,000 to 100,000 cells per microliter, leading to a condition known as a "leukemoid" or "leukemia-like" reaction. This heightened white blood cell response reflects the body's intensified effort to combat the infection or inflammatory stimulus.

1. Most bacterial infections induce selective increase in polymorphonuclear cells called (neutrophilia).

2. while parasitic infections & allergic responses characteristically induce eosinophilia.

3. Certain viruses, like infectious mononucleosis, mumps, & rubella cause selective↑ in lymphocytes (lymphocytosis).

4. However, most viral infections, rickettsial, protozoal, & certain types of bacterial infections (e.g., typhoid fever), are associated with a

5. Decreased number of circulating WBC called (leucopenia)

6. Severe bacterial infections (sepsis), especially by gram- negative bacteria stimulate the production of huge quantities of several cytokoines, notably TNF, IL-1, IL-6, & IL-8, resulting in septic shock, which is usually fatal.

1) Exactly, most bacterial infections lead to a selective increase in polymorphonuclear cells, specifically neutrophils. Neutrophilia is a common response observed in the blood during bacterial infections, reflecting the body's attempt to mobilize and deploy these white blood cells to the site of infection to combat the invading bacteria. Neutrophils are crucial components of the innate immune system and play a key role in phagocytosing and destroying bacteria.

بالضبط، تؤدي معظم الالتهابات البكتيرية إلى زيادة انتقائية في الخلايا متعددة الأشكال، وتحديدًا العدلات. العدلات هي استجابة شائعة يتم ملاحظتها في الدم أثناء الالتهابات البكتيرية، مما يعكس محاولة الجسم لتعبئة ونشر خلايا الدم البيضاء هذه في موقع العدوى لمكافحة البكتيريا الغازية. تعد العدلات مكونات مهمة في جهاز المناعة الفطري وتلعب دورًا رئيسيًا في البلعمة وتدمير البكتيريا.

2) in the case of parasitic infections and allergic responses, eosinophilia is a characteristic response. Eosinophils, a type of white blood cell, increase in number during these conditions. Eosinophils are particularly effective against parasites and are involved in the immune response against certain allergens. Therefore, an elevated eosinophil count, known as eosinophilia, is often indicative of parasitic infections or allergic reactions. This response is part of the body's efforts to defend against parasites and modulate immune responses in the context of allergies.

في حالة الالتهابات الطفيلية والاستجابات التحسسية، فإن كثرة اليوزينيات هي استجابة مميزة. يزداد عدد الحمضات، وهي نوع من خلايا الدم البيضاء، خلال هذه الظروف. الحمضات فعالة بشكل خاص ضد الطفيليات وتشارك في الاستجابة المناعية ضد بعض مسببات الحساسية. لذلك، فإن ارتفاع عدد اليوزينيات، المعروف باسم فرط الحمضات، غالبًا ما يشير إلى الإصابة بالعدوى الطفيلية أو تفاعلات الحساسية. هذه الاستجابة هي جزء من جهود الجسم للدفاع ضد الطفيليات وتعديل الاستجابات المناعية في سياق الحساسية.

3) Absolutely, certain viruses, including those responsible for infectious mononucleosis (e.g., Epstein-Barr virus), mumps, and rubella, can induce a selective increase in lymphocytes, a condition known as lymphocytosis. During these viral infections, there is a proliferation of lymphocytes in the bloodstream. Lymphocytes are a type of white blood cell critical to the adaptive immune response, and their increased presence reflects the immune system's active response to combat the viral pathogens.

بالتأكيد، يمكن لبعض الفيروسات، بما في ذلك تلك المسؤولة عن عدد كريات الدم البيضاء المعدية (على سبيل المثال، فيروس ابشتاين بار)، والنكاف، والحصبة الألمانية، أن تحدث زيادة انتقائية في الخلايا الليمفاوية، وهي حالة تعرف باسم كثرة الخلايا اللمفاوية. خلال هذه الالتهابات الفيروسية، هناك انتشار للخلايا الليمفاوية في مجرى الدم. الخلايا الليمفاوية هي نوع من خلايا الدم البيضاء المهمة للاستجابة المناعية التكيفية، ويعكس وجودها المتزايد الاستجابة النشطة للجهاز المناعي لمكافحة مسببات الأمراض الفيروسية.

4) Decreased number of circulating WBC called leucopenia. Leucopenia is a phenomenon where there is a reduced count of white blood cells in the blood. This can occur in various infections, including most viral infections, certain bacterial infections (such as typhoid fever), and diseases caused by rickettsiae or protozoa. The decreased white blood cell count is often a reflection of the impact of these infections on the bone marrow or the destruction of white blood cells in the circulation.

انخفاض عدد كريات الدم البيضاء المنتشرة والتي تسمى قلة الكريات البيض. قلة الكريات البيض هي ظاهرة حيث يوجد انخفاض في عدد خلايا الدم البيضاء في الدم. يمكن أن يحدث هذا في حالات العدوى المختلفة، بما في ذلك معظم حالات العدوى الفيروسية، وبعض أنواع العدوى البكتيرية (مثل حمى التيفوئيد)، والأمراض التي تسببها الركتسيا أو الأوليات. غالبًا ما يكون انخفاض عدد خلايا الدم البيضاء انعكاسًا لتأثير هذه الالتهابات على نخاع العظم أو تدمير خلايا الدم البيضاء في الدورة الدموية.

6) Indeed, severe bacterial infections, particularly those caused by gram-negative bacteria, can trigger an intense immune response leading to the production of significant quantities of various cytokines. Notably, Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Interleukin-8 (IL-8) are among the key cytokines involved.

This robust cytokine release is associated with a condition known as sepsis, a systemic inflammatory response to infection. In severe cases, this can progress to septic shock, a life-threatening condition characterized by a profound drop in blood pressure, multiple organ failure, and a high risk of fatality. Prompt and aggressive medical intervention is crucial to managing septic shock and improving the chances of survival.

في الواقع، يمكن للعدوى البكتيرية الشديدة، وخاصة تلك التي تسببها البكتيريا سالبة الجرام، أن تؤدي إلى استجابة مناعية مكثفة تؤدي إلى إنتاج كميات كبيرة من السيتوكينات المختلفة. ومن الجدير بالذكر أن عامل نخر الورم (TNF)، والإنترلوكين-1 (IL-1)، والإنترلوكين-6 (IL-6)، والإنترلوكين-8 (IL-8) من بين السيتوكينات الرئيسية المعنية.

ويرتبط هذا الإطلاق القوي للسيتوكينات بحالة تعرف باسم الإنتان، وهي استجابة التهابية جهازية للعدوى. في الحالات الشديدة، يمكن أن يتطور هذا إلى الصدمة الإنتانية، وهي حالة تهدد الحياة وتتميز بانخفاض عميق في ضغط الدم، وفشل العديد من الأعضاء، وارتفاع خطر الوفاة. يعد التدخل الطبي الفوري والقوي أمرًا بالغ الأهمية لإدارة الصدمة الإنتانية وتحسين فرص البقاء على قيد الحياة.

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Acute phase response**
  - Decreased appetite,
  - altered sleep patterns and
  - changes in plasma concentrations of:
- **Acute phase proteins**:
  - C-reactive protein (CRP) (Clinically useful)
  - α_1 antitrypsin
  - Haptoglobin
  - Fibrinogen
  - Serum amyloid A protein SAA

SUMMARY

Systemic Effects of Inflammation

- Fever: cytokines (TNF, IL-1) stimulate production of prostaglandins in hypothalamus
- Production of acute-phase proteins: C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells
- Leukocytosis: cytokines (CSFs) stimulate production of leukocytes from precursors in the bone marrow
- In some severe infections, septic shock: fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities; induced by high levels of TNF

Healing & Repair

Introduction :

When injury & any associated acute inflammatory response has resulted in necrosis of specialized cells and damage to the surrounding matrix , the host response must include attempts at replacement of the dead cells by healthy tissues.

This response is referred to as ***healing*** , and comprises two processes:

1 ***Regeneration :*** replacement of the specialized cells by proliferation of those surviving. Liver مثل

2 ***Connective tissue response :*** called ***repair*** , characterized by the formation of ***granulation tissue*** and its subsequent maturation i.e. ***fibrous scar formation***

which is highly vascularized connective tissue.

Matrix لتصليح ال

ويكون من Fibers.

granulation ← عن طريق تكوين tissue.

Fibers ندبة من

collagen وعالبًا

In the aftermath of injury and the accompanying acute inflammatory response, where necrosis of specialized cells and damage to the surrounding matrix have occurred, the host's response involves the imperative task of replacing the dead cells with healthy tissues. This pivotal response is aptly termed "healing" and encompasses two distinct processes:

1. **Regeneration:** This involves the replacement of the specialized cells by the proliferation of those cells that have managed to survive the injury. Regeneration is the body's inherent mechanism to restore the tissue to its normal structure and function.

2. **Connective Tissue Response (Repair):** Referred to as repair, this process is characterized by the formation of granulation tissue. Subsequently, this newly formed tissue undergoes maturation, ultimately leading to the development of fibrous scar tissue. Repair is a vital mechanism when regeneration alone is insufficient or not possible, ensuring structural integrity is maintained even if the tissue does not fully regain its original functional capacity.

- Although the fibrous scar is not normal, it **provides enough structural stability** that the injured tissue is able to function
- Commonly, repair involves **a combination** of both regeneration & scar formation in varying degrees.

Fibrosis: describe the extensive deposition of **collagen** that occurs in the organs as a consequence of chronic inflammation, or infarction, e.g., myocardium, lungs, liver, kidney, & other organs.

If fibrosis develops in a tissue space occupied by an inflammatory exudate it is called **organization** (e.g., **organizing pneumonia, organizing pleurisy**).

1) Absolutely, while fibrous scar tissue may not replicate the exact structure of the original tissue, it plays a crucial role in providing sufficient structural stability. This stability allows the injured tissue to function, albeit not at its original capacity.

In many cases of repair, there is a dynamic interplay between regeneration and scar formation. The extent to which each process contributes varies depending on factors such as the type and severity of the injury, the tissue involved, and the overall regenerative capacity of the specific tissue. This combination of regeneration and scar formation is a pragmatic strategy employed by the body to restore functionality and maintain structural integrity in response to injury and damage.

2) Fibrosis is characterized by the extensive deposition of collagen in organs, often as a consequence of chronic inflammation or infarction. This process can affect various organs such as the myocardium, lungs, liver, kidneys, and others.

When fibrosis occurs in a tissue space previously occupied by an inflammatory exudate, it is referred to as organization. For example, terms like "organizing pneumonia" and "organizing pleurisy" are used to describe instances where fibrotic changes are observed in the resolution of inflammatory conditions in the lungs or pleura, respectively. Organization involves the restructuring of tissue through the deposition of collagen, marking a reparative response that aims to restore the affected area but can lead to altered tissue architecture and function.

To understand repair, we have to know the

(1) Control of cell proliferation .

(2) The roles of stem cells (SC) in tissue homeostasis.

(3) Functions of the Extra Cellular Matrix (EXM) & how it is involved in repair.

(4) The roles of Growth Factors (GF) in the proliferation of different cell types involved in repair.

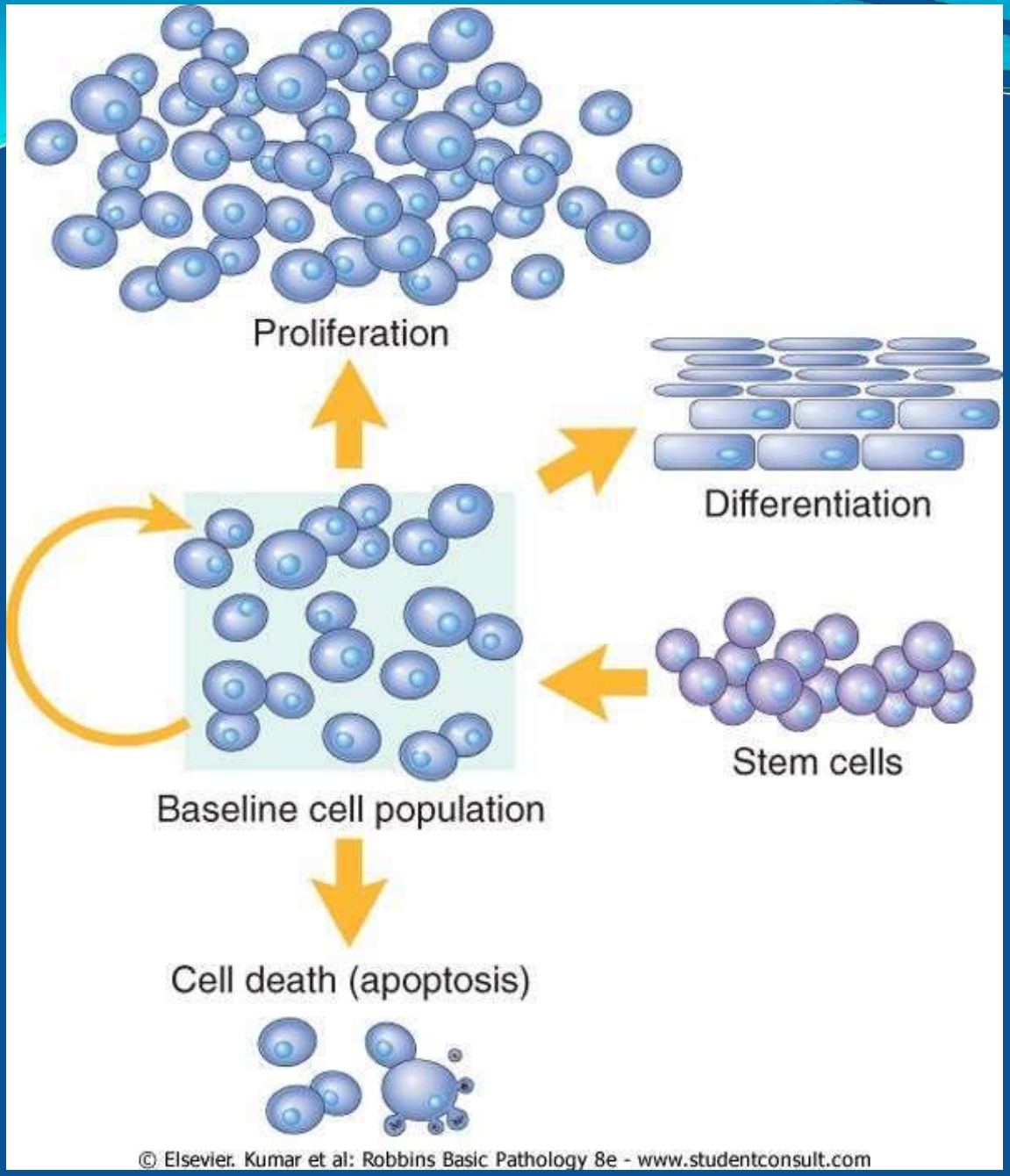
I- The Cell Cycle

The key process in the proliferation of cells, are DNA replication & mitosis. The sequence of events that control these 2 processes is known as the cell cycle.

The cell cycle consists of the:

(1) Presynthetic growth phase 1 (G1)
(2) DNA - synthetic phase , or (S)
(3) Premitotic growth phase 2 (G2)
(4) Mitotic phase (M).

انتاج بروتينات تحتاجها في ال S phase.
DNA replication
تصنع بروتينات تحتاجها بال M phase
mitosis.



F 57 : MECHANISMS REGULATING CELL POPULATION.

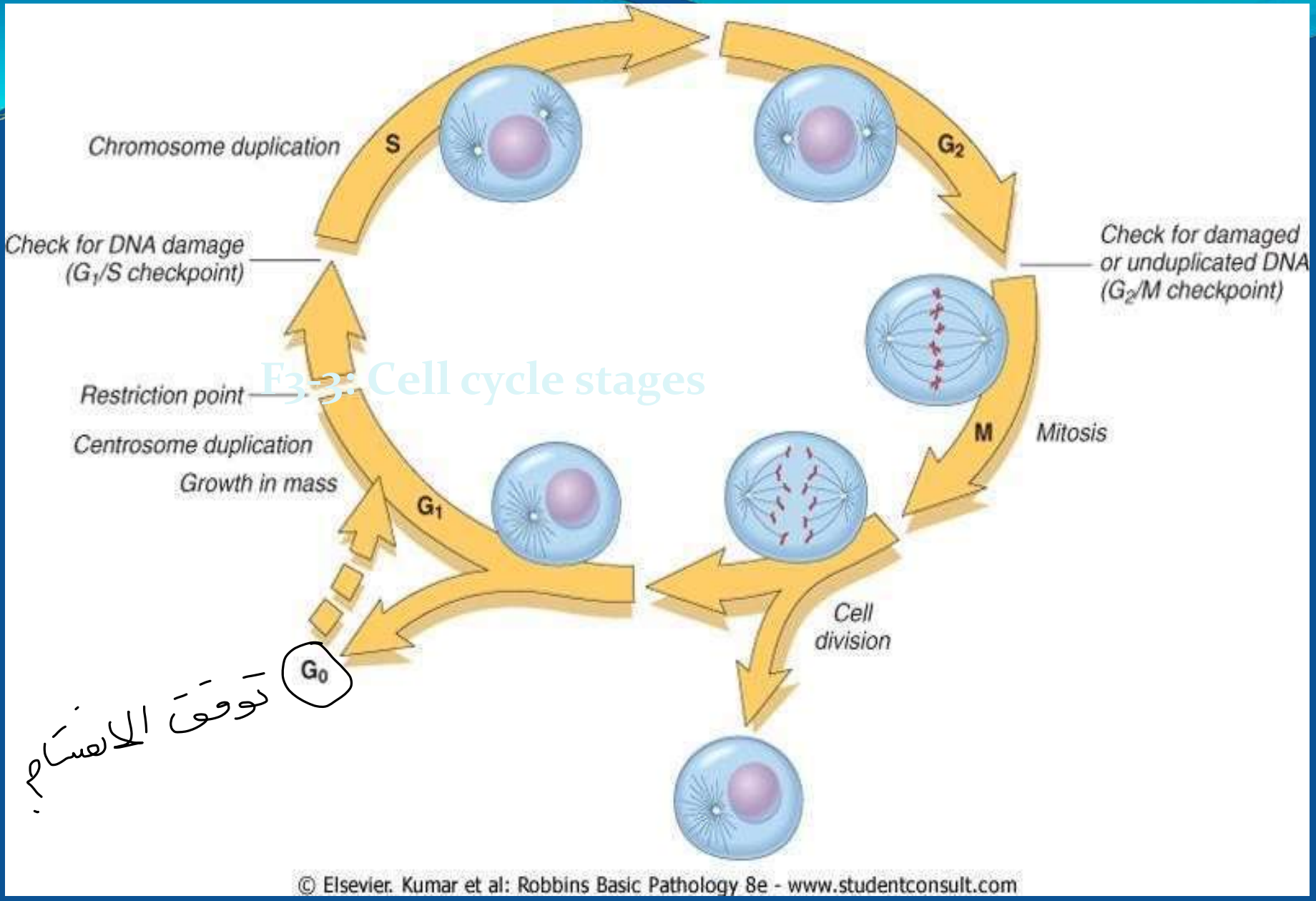


Figure 58 : Cell cycle . Diagrammatic view .

Somatic cells are divided into

- ***Labile cells :*** These cells are capable of regeneration , they have short life span and can multiply throughout life under normal conditions, like skin epidermal cells , gastro intestinal tract, respiratory tract , genitor urinary tract lining epithelial cells & bone marrow cells , after injury these cells under go regeneration with complete restoration of the normal architecture particularly if the injury is mild and transient.

لا تتجدد الا اذا اصابها damage

- ***Stable cells*** **:** These cells undergo multiplication during embryogenesis , but then cease multiplication when growth ceases. They have longer life span and slower mitotic rate.

They retain their mitotic activity during adult life and can undergo proliferation when stimulated after injury, so that some regeneration of dead tissue occurs in such cells like liver cells , renal , adrenal, pancreatic cells also the fibroblasts and osteoblasts.

موقت
يتوقفوا لما توقف مرحلة النمو

Liver cirrhosis

اذا اصابها damage in non parenchymal cells وكان severe مفهوم ممكن ما بيرتجدد ويصير

- ***Permanent cells*** Such cells are highly specialized like neurons ,the myocardial & the striated muscle cells .They have very long life span and no mitotic activity, once injured they never regenerate .

لما يصير damage بتجي مكانها Fiberes

التصليح الوصمي ← CT response ← scare formation

II- Role of Stem cells :

Stem Cells (SC) master cells of body

In most continuously dividing tissues, the mature cells are terminally differentiated & short-lived تتمايز .

As mature cells die in these tissues, they are replaced by the differentiation of cells generated from their Stem Cells .

Therefore, there is a homeostatic equilibrium between the: توازن بين التصنيع والموت .

(a) Replication & differentiation of SC, &

(b) The death of the mature fully differentiated cells.

Skin epidermis & the GIT epithelium, are good examples . In both, SC have been identified near the basal layer of the epithelium.

In actively dividing tissues, mature cells are often terminally differentiated and short-lived. To maintain a balance between cell loss and replenishment, stem cells play a crucial role. As mature cells die, they are replaced through the replication and differentiation of stem cells. This dynamic equilibrium exists between:

(a) Replication and differentiation of stem cells, and
(b) The death of mature, fully differentiated cells.

Examples such as the skin epidermis and the gastrointestinal (GIT) epithelium illustrate this phenomenon well. In these tissues, stem cells are typically located near the basal layer of the epithelium, ensuring a continuous process of cell renewal to sustain tissue integrity and function.

Stem Cells are characterized by two important properties:

A. . **Self-renewal capacity**

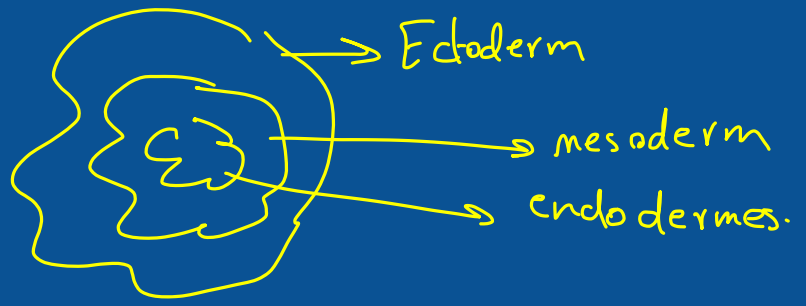
B. . **Asymmetric replication,**

which means, that after each cell division some progeny enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity.

SC with the capacity to generate multiple cell lineages (pluripotent Stem Cells)

Stem cells are of two kinds :

1- Embryonic stem cells (ES cells) : These are the most undifferentiated stem cells , they are present in the inner cell mass of the blastocyst , and have extensive cell renewal capacity . Under apropriate culture conditions ES cell can be induced to form cells of all three germ layers ,like neurons, cardiac myocytes , liver cells ...etc .



Stem cells possess two critical properties:

A. **Self-renewal capacity:**
Stem cells can replicate themselves, ensuring a continuous source for the generation of new cells.

B. **Asymmetric replication:**
This means that after each cell division, some progeny cells follow a differentiation pathway, specializing into specific cell types, while others retain their undifferentiated state, preserving the self-renewal capacity.

Stem cells with the ability to generate multiple cell lineages are termed pluripotent stem cells. There are two main types of stem cells:

1. **Embryonic Stem Cells (ES cells):**
- These are the most undifferentiated stem cells.
- Found in the inner cell mass of the blastocyst during embryonic development.
- Possess extensive cell renewal capacity.
- Under appropriate culture conditions, ES cells can be induced to differentiate into cells representing all three germ layers, including neurons, cardiac myocytes, liver cells, and more.

تمتلك الخلايا الجذعية خاصيتين مهمتين:

أ. **القدرة على التجديد الذاتي:**
يمكن للخلايا الجذعية أن تكرر نفسها، مما يضمن مصدرًا مستمرًا لتوليد خلايا جديدة.

ب. **النسخ غير المتماثل:**
وهذا يعني أنه بعد كل انقسام للخلية، تتبع بعض الخلايا السليلة مسارًا للتمايز، وتتخصص في أنواع معينة من الخلايا، بينما تحتفظ خلايا أخرى بحالتها غير المتمايزة، مما يحافظ على القدرة على التجديد الذاتي.

تسمى الخلايا الجذعية التي لديها القدرة على توليد سلالات خلايا متعددة بالخلايا الجذعية متعددة القدرات. هناك نوعان رئيسيان من الخلايا الجذعية:

1. **الخلايا الجذعية الجنينية (خلايا ES):**
- هذه هي الخلايا الجذعية الأكثر غير متمايزة.
- توجد في الكتلة الخلوية الداخلية للكيسة الأريمية أثناء التطور الجنيني.
- يمتلك قدرة واسعة على تجديد الخلايا.
- في ظل ظروف الاستزراع المناسبة، يمكن حث الخلايا الجذعية الجنينية على التمايز إلى خلايا تمثل الطبقات الجرثومية الثلاث، بما في ذلك الخلايا العصبية وخلايا عضلة القلب وخلايا الكبد والمزيد.

2- Adult stem cells : also called **tissue stem cells**, these are less undifferentiated than ES cells and are found among differentiated tissues & organs .

Although like ES cells have self-renewal capacity , but it is a limited property , and their lineage potential i.e. ability to give rise to specialized cells restricted to some or all the differentiated cells of that tissue or organ . These are present in the **bone marrow** & several other tissues of the adult individuals.

The most extensively studied **tissue or adult stem cells** are the **hematopoietic stem cells** found in the bone marrow , as well as from peripheral blood , after mobilization by certain cytokines **like granulocyte colony- stimulating factor (G-CSF)**

Adult stem cells, also known as tissue stem cells, are less undifferentiated compared to embryonic stem cells (ES cells). They are primarily located among differentiated tissues and organs in adult individuals. While they share the self-renewal capacity with ES cells, this property is limited in adult stem cells. Additionally, their lineage potential—the ability to give rise to specialized cells—is typically restricted to some or all of the differentiated cells within the tissue or organ where they reside.

Adult stem cells are found in various tissues, including the bone marrow and several other organs. One of the most extensively studied types of adult stem cells is hematopoietic stem cells, which are present in the bone marrow and can also be obtained from peripheral blood after mobilization using specific cytokines like granulocyte colony-stimulating factor (G-CSF).

الخلايا الجذعية البالغة، والمعروفة أيضًا باسم الخلايا الجذعية النسيجية، أقل تباينًا مقارنة بالخلايا الجذعية الجنينية (خلايا ES). وهي تقع في المقام الأول بين الأنسجة والأعضاء المتمايزة لدى الأفراد البالغين. على الرغم من أنها تشترك في القدرة على التجديد الذاتي مع الخلايا الجذعية الجنينية، إلا أن هذه الخاصية محدودة في الخلايا الجذعية البالغة. بالإضافة إلى ذلك، فإن إمكانات نسبها - القدرة على إنشاء خلايا متخصصة - تقتصر عادةً على بعض أو كل الخلايا المتمايزة داخل الأنسجة أو العضو الذي تعيش فيه.

توجد الخلايا الجذعية البالغة في أنسجة مختلفة، بما في ذلك نخاع العظم والعديد من الأعضاء الأخرى. أحد أكثر أنواع الخلايا الجذعية البالغة التي تمت دراستها على نطاق واسع هي الخلايا الجذعية المكونة للدم، والتي توجد في نخاع العظم ويمكن الحصول عليها أيضًا من الدم المحيطي بعد التعبئة باستخدام سيتوكينات محددة مثل عامل تحفيز مستعمرة الخلايا المحببة (G-CSF).

Bone marrow SC have very broad differentiation capabilities . They can differentiate into all blood cells lineage as well as being able to generate fat, muscle, cartilage, bone, & endothelium (EC).

In clinical practice , marrow stem cells are used for treatment of leukemia & lymphoma . → spinal cord injury → ALZheimar parkensons → لبعض الحالات stem cells بال

The ability to identify & isolate stem cells have given rise to the new field of **(Regenerative Medicine)** its main goal, is the regeneration & repopulation of damaged organs (e.g., Myocardial Infarction) using **Embryonal Stem cells or adult SC.** → Form Embryonic stem cells myocardial cells

One of the most exciting prospects in this field is of SC therapy known as **(therapeutic cloning) .** افاق

Bone marrow stem cells exhibit broad differentiation capabilities, able to give rise to all blood cell lineages and generate various tissues such as fat, muscle, cartilage, bone, and endothelium (EC). In clinical applications, marrow stem cells are utilized for the treatment of conditions like leukemia and lymphoma.

The ability to identify and isolate stem cells has paved the way for the emerging field of Regenerative Medicine. The primary goal of this field is the regeneration and repopulation of damaged organs, such as in cases of myocardial infarction. This can be achieved using embryonic stem cells or adult stem cells.

One particularly promising avenue in regenerative medicine is stem cell therapy, including a technique known as therapeutic cloning. This approach involves creating embryonic stem cells that are genetically identical to a patient's cells, holding significant potential for personalized and effective medical treatments.

تُظهر الخلايا الجذعية لنخاع العظم قدرات تمايز واسعة، قادرة على توليد جميع سلالات خلايا الدم وتوليد أنسجة مختلفة مثل الدهون والعضلات والغضاريف والعظام والبطانة (EC). في التطبيقات السريرية، يتم استخدام الخلايا الجذعية النخاعية لعلاج حالات مثل سرطان الدم وسرطان الغدد الليمفاوية.

لقد مهدت القدرة على تحديد الخلايا الجذعية وعزلها الطريق أمام مجال الطب التجديدي الناشئ. الهدف الأساسي لهذا المجال هو تجديد وإعادة إعمار الأعضاء التالفة، كما هو الحال في حالات احتشاء عضلة القلب. ويمكن تحقيق ذلك باستخدام الخلايا الجذعية الجنينية أو الخلايا الجذعية البالغة.

أحد السبل الواعدة بشكل خاص في الطب التجديدي هو العلاج بالخلايا الجذعية، بما في ذلك تقنية تعرف باسم الاستنساخ العلاجي. يتضمن هذا النهج إنشاء خلايا جذعية جنينية متطابقة وراثيًا مع خلايا المريض، مما يحمل إمكانات كبيرة للعلاجات الطبية الشخصية والفعالة.

The main steps involved in therapeutic cloning, using ES cells for cell therapy .

In this procedure:

(1)The **diploid nucleus** of a cell (e.g., WBC) from a patient (e.g., with MI or CVA) is introduced into **an enucleated oocyte.**

cardio vascular accident.

(2)The oocyte is activated & the zygote divides to become a **blastocyst** containing donor DNA.

(3) The blastocyst is dissociated to obtain **ES cells** ;

(4)ES cells are capable of differentiating into various tissues (e.g., myocytes or neurons), either in culture or after transplantation into the donor.

The goal is to repopulate the damaged heart or brain cells of the patient, **using the patient's cells himself, thus avoiding immunologic rejection.**

Patient DNA → تجنباً للرفض المناعي

In therapeutic cloning using embryonic stem (ES) cells for cell therapy, the main steps involve:

1. **Introduction of Patient's Nucleus:**
- The diploid nucleus of a cell, for instance, a white blood cell (WBC) from the patient (e.g., with myocardial infarction or cerebrovascular accident), is introduced into an enucleated oocyte.

2. **Activation and Division:**
- The oocyte, now containing the patient's DNA, is activated, and the zygote undergoes division to form a blastocyst.

3. **Obtaining ES Cells:**
- The blastocyst is dissociated to obtain embryonic stem (ES) cells, which carry the donor DNA.

4. **Differentiation of ES Cells:**
- ES cells, with their capability to differentiate into various tissues such as myocytes or neurons, can be induced to do so either in culture or after transplantation into the donor.

The ultimate goal of therapeutic cloning is to repopulate damaged tissues, like the heart or brain cells of the patient, using the patient's own cells. This approach aims to circumvent immunologic rejection, as the cells are derived from the patient's own genetic material.

في الاستنساخ العلاجي باستخدام الخلايا الجذعية الجنينية للعلاج بالخلايا، تتضمن الخطوات الرئيسية ما يلي:

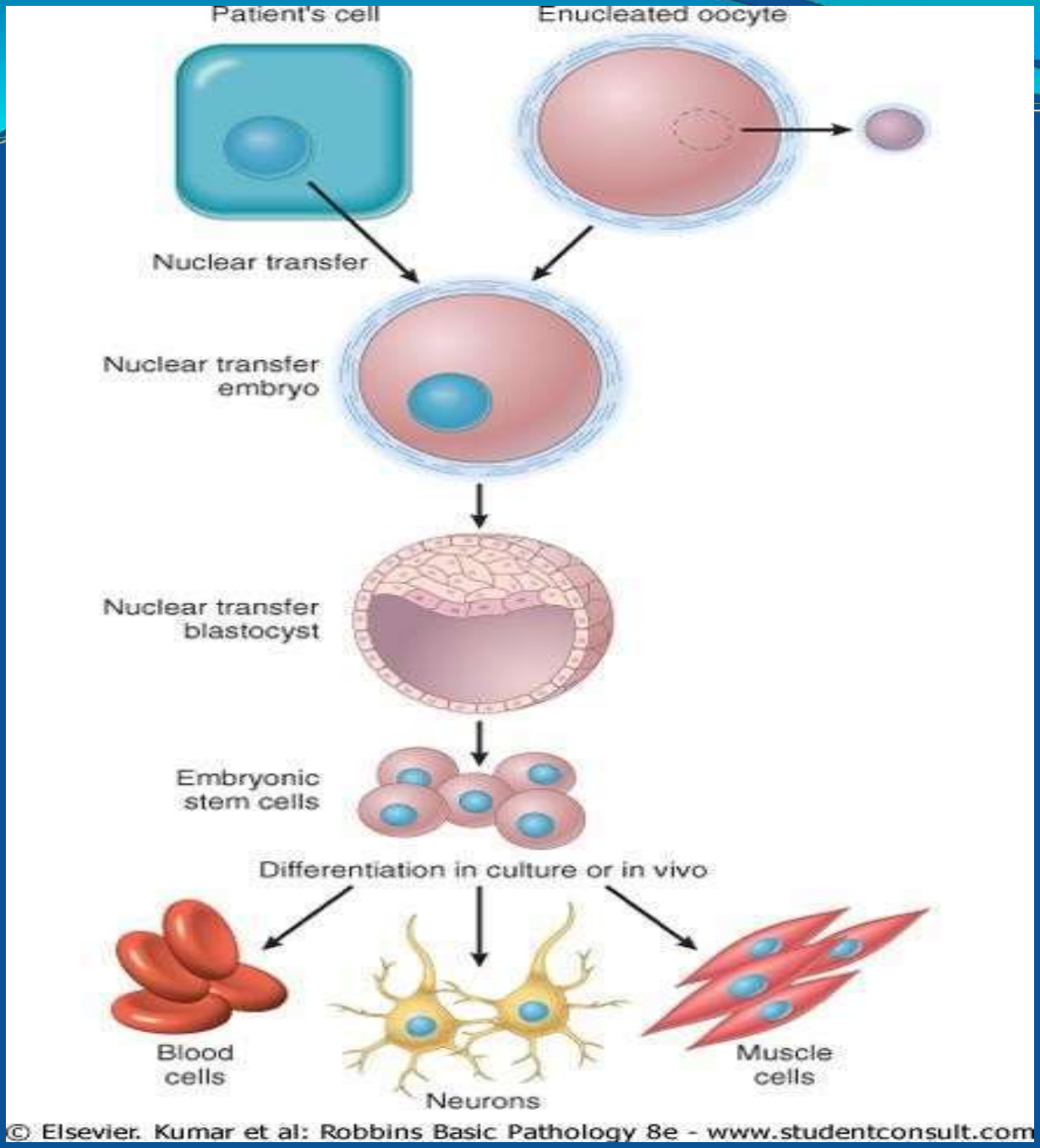
1. **مقدمة لنواة المريض:**
- يتم إدخال النواة الثنائية الصبغية لخلية، على سبيل المثال، خلية دم بيضاء (WBC) من المريض (على سبيل المثال، احتشاء عضلة القلب أو حادث وعائي دماغي)، في بويضة منزوعة النواة.

2. **التنشيط والتقسيم:**
- يتم تنشيط البويضة، التي تحتوي الآن على الحمض النووي للمريض، ويخضع اللاقحة للانقسام لتكوين الكيسة الأريمية.

3. **الحصول على الخلايا الجذعية الجنينية:**
- يتم فصل الكيسة الأريمية للحصول على الخلايا الجذعية الجنينية التي تحمل الحمض النووي للمتبرع.

4. **تمايز الخلايا الجذعية الجنينية:**
- يمكن حث الخلايا الجذعية الجنينية، بما لديها من قدرة على التمايز إلى أنسجة مختلفة مثل الخلايا العضلية أو الخلايا العصبية، على القيام بذلك إما في المزرعة أو بعد زرعها في المتبرع.

الهدف النهائي للاستنساخ العلاجي هو إعادة ملء الأنسجة التالفة، مثل خلايا القلب أو الدماغ للمريض، باستخدام خلايا المريض نفسه. ويهدف هذا النهج إلى التحايل على الرفض المناعي، حيث أن الخلايا مشتقة من المادة الوراثية الخاصة بالمريض.



F 59 : Steps involved in therapeutic cloning, using embryonic stem (ES) cells for cell therapy.

III- Extra cellular Matrix (ECM) & Cell-Matrix Interactions

ECM is a dynamic, constantly remolding macromolecular complex, synthesized locally, arrange into a network that surrounds cells, & constituting a significant proportion of any tissue. ECM sequesters water, providing firmness to soft tissue & minerals, giving rigidity to bone.

By supplying cell adhesion & a reservoir for Growth Factors (GF) , ECM regulate the movement, proliferation, & differentiation of the cells within it

The Extracellular Matrix (ECM) is a dynamic macromolecular complex that undergoes constant remodeling. Locally synthesized, it forms a network surrounding cells, comprising a substantial portion of any tissue. The ECM serves various functions, including sequestering water to provide firmness to soft tissues and incorporating minerals to impart rigidity to bone.

Moreover, the ECM plays a pivotal role in cellular interactions. It supplies points for cell adhesion and acts as a reservoir for Growth Factors (GF). This regulation of cell adhesion and the provision of growth factor reservoirs enable the ECM to control essential cellular processes, including cell movement, proliferation, and differentiation within the tissue. The intricate interplay between cells and their surrounding ECM is crucial for maintaining tissue structure and function.

المصفوفة خارج الخلية (ECM) عبارة عن مجمع جزيئي ديناميكي يخضع لعملية إعادة تشكيل مستمرة. يتم تصنيعه محليًا، ويشكل شبكة تحيط بالخلايا، تشتمل على جزء كبير من أي نسيج. يؤدي ECM وظائف مختلفة، بما في ذلك عزل المياه لتوفير الصلابة للأنسجة الرخوة ودمج المعادن لإضفاء الصلابة على العظام.

علاوة على ذلك، يلعب ECM دورًا محوريًا في التفاعلات الخلوية. يوفر نقاط التصاق الخلايا ويعمل كمستودع لعوامل النمو (GF). هذا التنظيم لالتصاق الخلايا وتوفير خزانات عامل النمو يمكّن ECM من التحكم في العمليات الخلوية الأساسية، بما في ذلك حركة الخلايا وانتشارها وتمايزها داخل الأنسجة. يعد التفاعل المعقد بين الخلايا وECM المحيطة بها أمرًا بالغ الأهمية للحفاظ على بنية الأنسجة ووظيفتها.

ECM occurs in 2 basic forms:

Interstitial matrix

& Basement Membrane.

Interstitial Matrix :

Present in: (1) the spaces between cells in connective tissue .

(2) between epithelium & the supportive vascular & smooth muscle structures.

Its major constituents are:

- fibrillar collagen (types I, II, III, V)
- nonfibrillar (IV) collagens
- fibronectin → helps in adhesion.
- elastin
- proteoglycan
- hyaluronate & others.

It is synthesized by mesenchymal cells (e.g fibroblasts) & tends to form a three-dimensional amorphous gel.

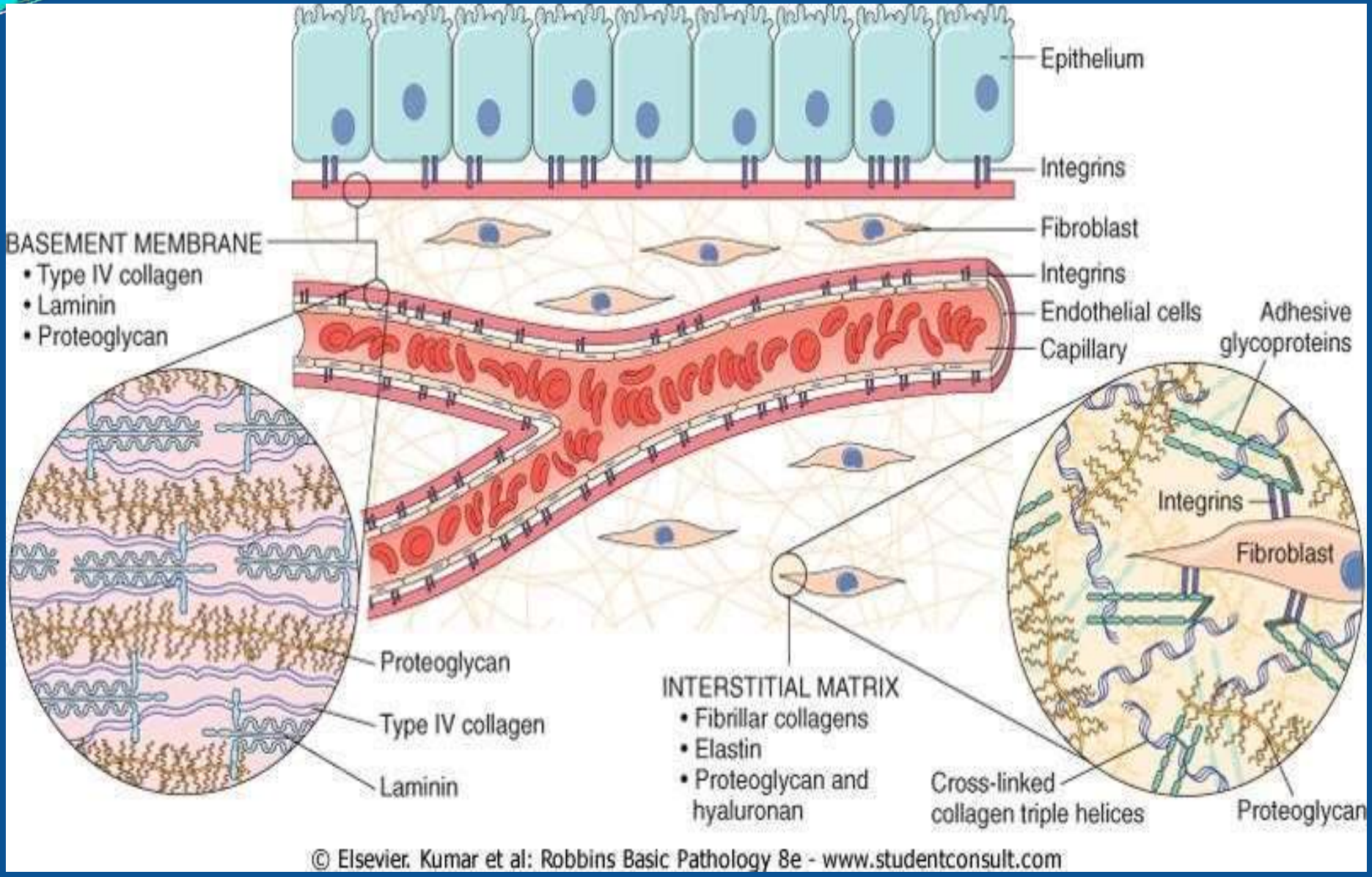
The Extracellular Matrix (ECM) exists in two fundamental forms: Interstitial Matrix and Basement Membrane.

Interstitial Matrix:
1. **Location:**
   - Found in the spaces between cells in connective tissue.
   - Also present between epithelium and the supportive vascular and smooth muscle structures.

2. **Major Constituents:**
   - Fibrillar collagen (types I, II, III, V)
   - Nonfibrillar collagen (IV)
   - Fibronectin
   - Elastin
   - Proteoglycan
   - Hyaluronate, and others.

3. **Synthesis:**
   - Synthesized by mesenchymal cells, such as fibroblasts.
   - Tends to form a three-dimensional amorphous gel, contributing to the structural integrity and resilience of the tissue.

F 60 : Major components of Extra Cellular Matrix (ECM)



Basement membrane (BM) :

The interstitial matrix in connective tissues becomes highly organized around epithelial cells Epithelial Cells & Smooth Muscle Cells forming the specialized BM.

BM lies (sits) beneath epithelium forming a plate - like **chicken wire mesh**.

BM major constituents are **laminin + amorphous non fibrillar type IV collagen , and proteoglycan .**

It is formed by the underlying mesenchymal cells & overlying epithelium.

The Basement Membrane (BM) is a specialized form of the interstitial matrix that becomes highly organized around epithelial cells and smooth muscle cells.

Characteristics of Basement Membrane (BM):
1. **Location:**
   - Lies beneath epithelium, forming a plate-like structure resembling a chicken-wire mesh.

2. **Major Constituents:**
   - Laminin
   - Amorphous, non-fibrillar type IV collagen
   - Proteoglycan

3. **Formation:**
   - Formed by the collaboration of cells and overlying epithelium.
   - This specialized structure provides crucial support and separation between different tissue compartments, contributing to tissue integrity and function.

Figure 61 : Bronchial mucosa showing basement membrane (arrows)

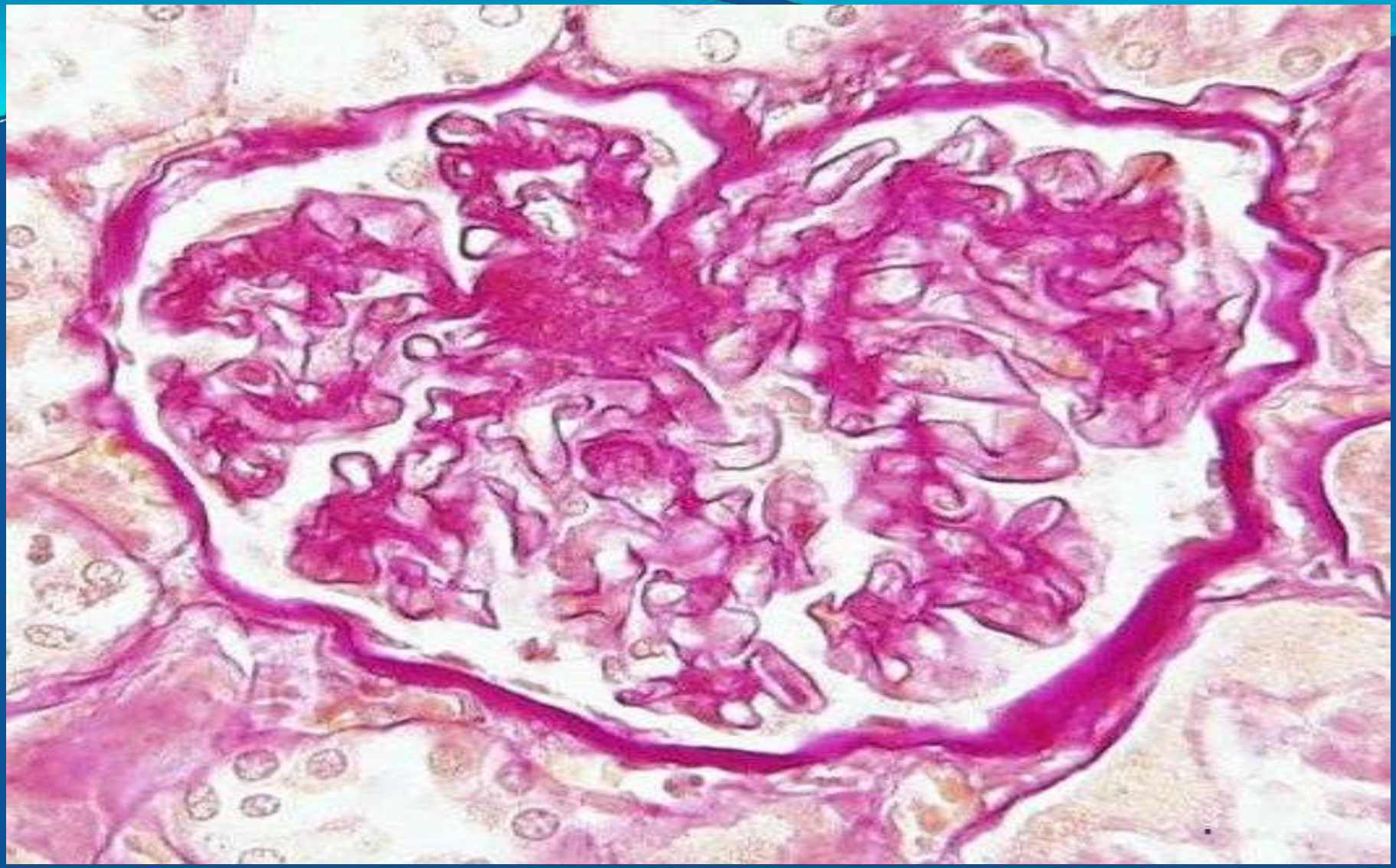


Figure 62 : Renal glomerulus showing basement membrane (pink colored)

Functions of ECM

(1) Mechanical support for Cell anchorage (fixation) + migration ± Maintenance of cell polarity

(2) Control of cell growth.

ECM components can regulate cell proliferation .

(3) Maintenance of cell differentiation.

Type of ECM proteins affects the degree of differentiation of the cells in the tissue, acting via cellular receptor of integrin family.

(4) Scaffolding for tissue renewal.

The maintenance of normal tissue structure requires BM for stromal scaffold.

(5) BM acts as a boundary between epithelium & underlying connective tissue .

(6) Storage & presentation of GFs like FGF & HGF, both are excreted & stored in the ECM in some tissues.

Hepatocyte G.F.

Fibroblast GF

the functions of the Extracellular Matrix (ECM) in tissue physiology:

1. **Mechanical Support:**
   - The ECM provides a structural framework offering mechanical support, anchoring cells in place, facilitating their migration, and ensuring the maintenance of cell polarity. This is crucial for the overall stability and organization of tissues.

2. **Cell Growth Control:**
   - ECM components play a pivotal role in controlling cell growth. They can either promote or inhibit cell proliferation, influencing the rate and extent of tissue development and repair.

3. **Cell Differentiation Maintenance:**
   - ECM proteins actively participate in maintaining cell differentiation. Different types of ECM influence the degree of specialization of cells within a tissue. Cellular receptors of the integrin family often mediate these effects.

4. **Scaffolding for Tissue Renewal:**
   - The ECM, especially through structures like the Basement Membrane (BM), acts as a scaffolding essential for tissue renewal. It provides the necessary support and structure for the maintenance of normal tissue architecture during the renewal process.

5. **Boundary Function:**
   - Serving as a boundary between epithelial and connective tissues, the ECM contributes to the organization and separation of distinct tissue compartments. This boundary function is essential for maintaining tissue integrity and preventing uncontrolled cell movements.

6. **Storage and Presentation of Growth Factors (GFs):**
   - The ECM serves as a reservoir for growth factors like Fibroblast Growth Factor (FGF) and Hepatocyte Growth Factor (HGF). These growth factors, when excreted and stored in the ECM, can be released in a controlled manner, influencing cellular responses and contributing to tissue repair and regeneration.

Collagen :

This is the most abundant of the matrix protein, it is synthesized by the fibroblasts & osteoblasts .

Collagens are fibrous structural proteins, that confer tensile strength .

The collagen s are composed of three separate polypeptide chains braided into rope-like triple helix . More than 30 types have been identified, some of which are unique to specific cells & tissues .

Can be fibrillar collagen like type I,II, III,&V .

Collagen types I & III form a major proportion of the connective tissue in healing wounds & particularly in scars.

The tensile strength of the fibrillar collagen derives from their cross-linking, which is the result of covalent bonds catalyzed by the enzyme lysyl-oxidase , his process requires vitamin C .

That is why individuals with vitamin C deficiency have skeletal deformities .

Other are non-fibrillar & may form :

(a) BM (type IV)

(b) or be component of other structures like intervertebral discs (type IX), or dermal-epidermal junctions (type VII).

various aspects of collagen and its significance in tissue physiology:

1. **Composition:**
   - Collagens are intricate structures composed of three polypeptide chains intertwined into a triple helix. This unique composition provides strength and resilience to the collagen fibers.

2. **Diversity of Collagen Types:**
   - The extensive diversity in collagen types, exceeding 30, allows for specialized functions in different tissues. Fibrillar collagens, such as type I, II, III, and V, contribute to the strength and structural integrity of various tissues.

3. **Role in Healing and Scarring:**
   - Collagen types I and III are particularly crucial in the context of wound healing. They form a significant proportion of the connective tissue during the healing process and are predominant in scar tissue formation.

4. **Mechanism of Tensile Strength:**
   - The tensile strength of fibrillar collagen is a result of cross-linking, where covalent bonds are formed. The enzyme lysyl-oxidase catalyzes this process. Notably, vitamin C is essential for this enzymatic activity, and deficiency can lead to weakened collagen and skeletal deformities.

5. **Non-Fibrillar Collagens:**
   - Beyond fibrillar collagens, non-fibrillar types, such as type IV, contribute to the formation of the Basement Membrane. Collagen types IX and VII play roles in structures like intervertebral discs and dermal-epidermal junctions, respectively.

6. **Genetic Defects and Associated Diseases:**
   - Genetic defects in collagen genes can result in conditions like Osteogenesis Imperfecta and Ehlers-Danlos syndrome. These disorders manifest with various abnormalities in connective tissues, impacting bones, skin, and other organs, underscoring the critical role of collagen in maintaining tissue integrity.

In summary, collagen's intricate structure, diverse types, and multifaceted roles make it a cornerstone in tissue physiology, influencing everything from wound healing to the maintenance of tissue structure and strength. The understanding of collagen's complexities is pivotal for comprehending and addressing various pathological conditions related to connective tissues.

ELASTIN

After physical stress, the ability of tissue to recoil & return to a baseline structure is conferred by elastic tissue, especially in the walls of large blood vessel (e g aorta, which must accommodate recurrent pulsatile blood flow), uterus, skin, & ligaments. Morphologically elastic fibers consist central core of elastin surrounded by meshwork of **fibrillin glycoprotein** . Defects in fibrillin synthesis leads to weakening of arterial walls & skeletal deformities like **Marfan's syndrome** .

PROTEOGLYCANS & HYALURONAN

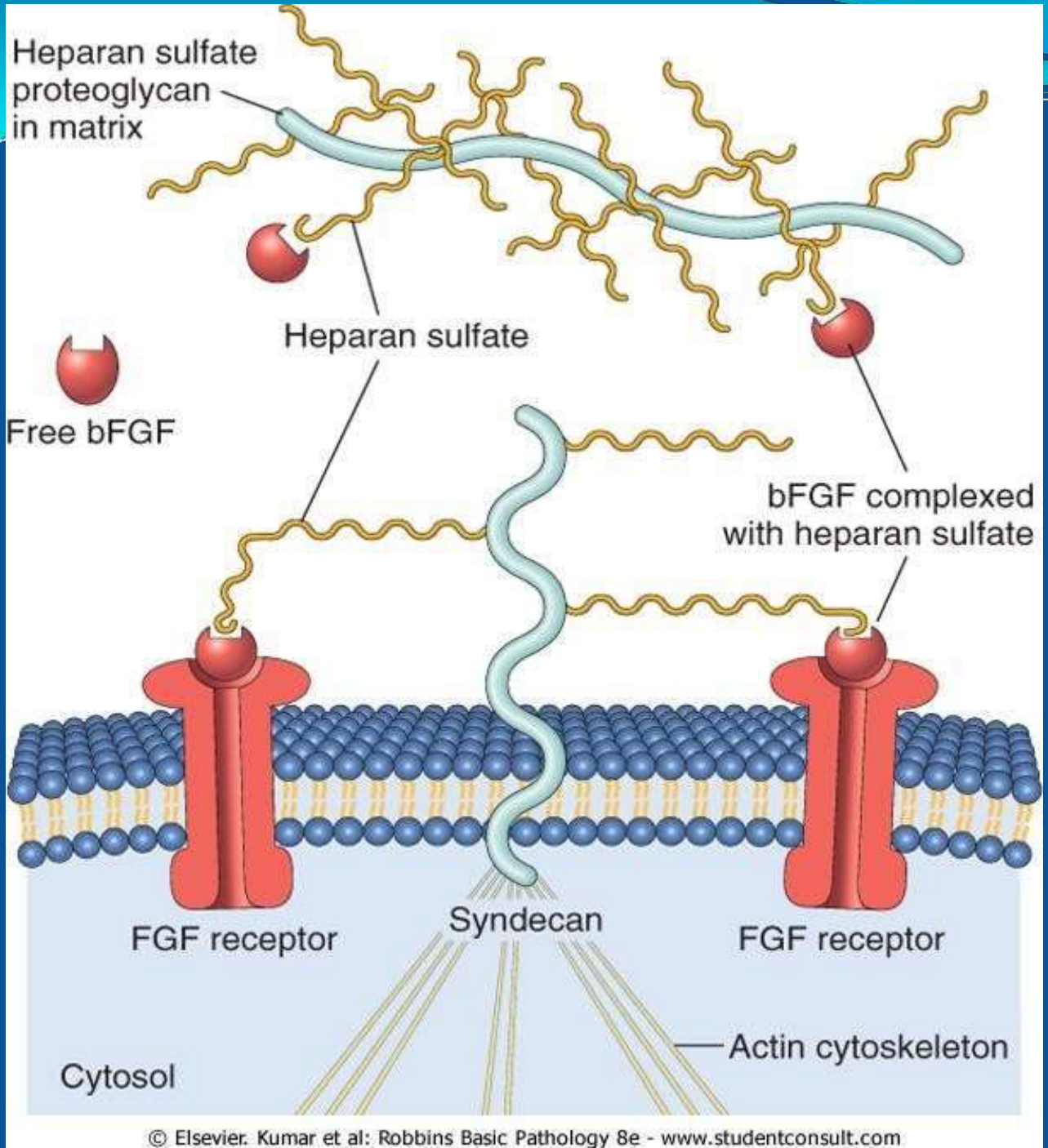
These are highly hydrated compressible gel conferring **resilience and lubrication** such as cartilage in joints .

They consist of long polysaccharides, called **glycosaminoglycans , or mucopolysaccharides ,** (examples are dermatan sulfate & heparan sulfate)

Also serve as **reservoirs** for Growth Factors s secreted into the ECM (e. g Fibroblast Growth Factor).

ELASTIN:
Elastin, a crucial component in tissues, enables them to recoil and regain their original structure after physical stress. This is particularly vital in large blood vessels (e.g., aorta), the uterus, skin, and ligaments. Morphologically, elastic fibers consist of a central core of elastin surrounded by a meshwork of the fibrillin glycoprotein. Deficiencies in fibrillin synthesis, as observed in Marfan's syndrome, can lead to weakened arterial walls and skeletal deformities, underscoring the essential role of elastin in maintaining tissue elasticity and integrity.

PROTEOGLYCANS & HYALURONAN:
Proteoglycans and hyaluronan play pivotal roles in maintaining tissue resilience and lubrication, especially in structures like joint cartilage. They are composed of long polysaccharides, known as glycosaminoglycans (or mucopolysaccharides), with examples including dermatan sulfate and heparan sulfate. Beyond providing structural support, these components serve as reservoirs for Growth Factors, such as Fibroblast Growth Factor, within the Extracellular Matrix (ECM). This dual functionality highlights their significance not only in sustaining tissue integrity but also in influencing cellular responses, contributing to processes like tissue repair and regeneration. The hydrated and compressible nature of this gel-like matrix is crucial for the proper functioning of various tissues, particularly those subject to mechanical stress.



F 63 : Proteoglycans in the ECM & on cells act as reservoirs for GF.